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(FILE 'HOME' ENTERED AT 14:43:49 ON 12 MAR 2003)

FILE 'EMBASE, BIOSIS, EUROPATFULL, JAPIO, ADISCTI, ADISINSIGHT, ADISNEWS, BABS, BIOBUSINESS, BIOCOMMERCE, BIOTECHNO, CANCERLIT, CAPLUS, CBNB, CEN, CIN, CONFSCI, DGENE, DIOGENES, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, DRUGUPDATES, EMBAL, ESBIOBASE, ...' ENTERED AT 14:44:10 ON 12 MAR 2003

L1 26731 S (LYMPHOKIN? OR IL-2 OR INTERLEUKIN? OR CYTOKIN?) AND (KILLER
L2 14124 S L1 AND (EPSTEIN-BARR OR EBV)
L3 10644 S L2 AND (EPSTEIN-BARR)

=> s l1 and (il-2 or interleukin?) (50a) (killer cell or killer cells or lymphocyte?) and (epstein-barr or ebv or cmv or cytomeg? or herpes or herpes simplex)
4 FILES SEARCHED...
12 FILES SEARCHED...
24 FILES SEARCHED...
30 FILES SEARCHED...
39 FILES SEARCHED...
49 FILES SEARCHED...
64 FILES SEARCHED...
L4 7332 L1 AND (IL-2 OR INTERLEUKIN?) (50A) (KILLER CELL OR KILLER CELLS OR LYMPHOCYTE?) AND (EPSTEIN-BARR OR EBV OR CMV OR CYTOMEG ? OR HERPES OR HERPES SIMPLEX)

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> s (lymphokin? or il-2 or interleukin? or cytokin?) and (killer cell or killer
cells or lymphocyte?) and (epstein-barr or ebv or cmv or cytomeg? or herpes or
herpes simplex)
   3 FILES SEARCHED...
  11 FILES SEARCHED...
  16 FILES SEARCHED...
  24 FILES SEARCHED...
  29 FILES SEARCHED...
  36 FILES SEARCHED...
  44 FILES SEARCHED...
  49 FILES SEARCHED...
  62 FILES SEARCHED...
L1       26731 (LYMPHOKIN? OR IL-2 OR INTERLEUKIN? OR CYTOKIN?) AND (KILLER
               CELL OR KILLER CELLS OR LYMPHOCYTE?) AND (EPSTEIN-BARR OR EBV
               OR CMV OR CYTOMEG? OR HERPES OR HERPES SIMPLEX)
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L1 26731 S (LYMPHOKIN? OR IL-2 OR INTERLEUKIN? OR CYTOKIN?) AND (KILLER
L2 14124 S L1 AND (EPSTEIN-BARR OR EBV)
L3 10644 S L2 AND (EPSTEIN-BARR)
L4 7332 S L1 AND (IL-2 OR INTERLEUKIN?) (50A) (KILLER CELL OR KILLER C
L5 1665 S L4 AND (AUTOLOGOUS OR AUTO LOGUOUS)
L6 1432 S L5 AND (EPSTEIN-BARR OR EBV OR (HERPES AND SIMPLEX))
L7 183 S (LYMPHOKIN? OR IL-2 OR INTERLEUKIN? OR CYTOKIN?) AND (AUTOLOG
L8 96 DUP REM L7 (87 DUPLICATES REMOVED)

=> s (il-2 or interleukin) (50a) (killer cell or killer cells or lyphocyte?) and (epstein-barr or ebv (herpes and simplex))

```
=> s (lymphokin? or il-2 or interleukin? or cytokin?) and (autologous or auto
logous) (50a) (killer cell or killer cells or lyphocyte?) and (epstein-barr or ebv
or cmv or cytomeg? or herpes or herpes simplex)
   4 FILES SEARCHED...
  12 FILES SEARCHED...
  22 FILES SEARCHED...
  30 FILES SEARCHED...
  39 FILES SEARCHED...
  49 FILES SEARCHED...
  63 FILES SEARCHED...
L7          183 (LYMPHOKIN? OR IL-2 OR INTERLEUKIN? OR CYTOKIN?) AND (AUTOLOGOUS
                 OR AUTO LOGOUS) (50A) (KILLER CELL OR KILLER CELLS OR LYPHOCYTE
                ?) AND (EPSTEIN-BARR OR EBV OR CMV OR CYTOMEG? OR HERPES OR
                HERPES SIMPLEX)

=> dup rem l7
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, BIOCOMMERCE, DGENE,
DIOGENES, DRUGLAUNCH, DRUGMONOG2, DRUGUPDATES, FEDRIP, INVESTEXT, KOSMET,
MEDICONF, NUTRACEUT, PHAR, PHARMAML, SYNTHLINE, USAN, CHEMLIST, FOREGE, HSDB,
MSDS-CCOHS, MSDS-OHS, RTECS'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L7
L8           96 DUP REM L7 (87 DUPLICATES REMOVED)
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=> s (il-2 or interleukin) (50a) (killer cell or killer cells or lyphocyte?) and
(epstein-barr or ebv or (herpes and simplex))
   4 FILES SEARCHED...
  12 FILES SEARCHED...
  27 FILES SEARCHED...
  38 FILES SEARCHED...
  47 FILES SEARCHED...
  57 FILES SEARCHED...
L9          790 (IL-2 OR INTERLEUKIN) (50A) (KILLER CELL OR KILLER CELLS OR
                LYPHOCYTE?) AND (EPSTEIN-BARR OR EBV OR (HERPES AND SIMPLEX))

=> dup rem l9
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, BIOCOMMERCE, DGENE,
DIOGENES, DRUGLAUNCH, DRUGMONOG2, DRUGUPDATES, FEDRIP, INVESTEXT, KOSMET,
MEDICONF, NUTRACEUT, PHAR, PHARMAML, SYNTHLINE, USAN, CHEMLIST, FOREGE, HSDB,
MSDS-CCOHS, MSDS-OHS, RTECS'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L9
L10          472 DUP REM L9 (318 DUPLICATES REMOVED)

=> d 1-472
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L10 ANSWER 315 OF 472 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 24
ACCESSION NUMBER: 96119657 EMBASE
DOCUMENT NUMBER: 1996119657
TITLE: Human **Epstein-Barr** virus (**EBV**)-specific cytotoxic T lymphocytes home preferentially to and induce selective regressions of autologous **EBV**-induced B cell lymphoproliferations in xenografted C.B-17 scid/scid mice.
AUTHOR: Lacerda J.F.; Ladanyi M.; Louie D.C.; Fernandez J.M.; Papadopoulos E.B.; O'Reilly R.J.
CORPORATE SOURCE: MSKCC, 1275 York Avenuee,New York, NY 10021, United States
SOURCE: Journal of Experimental Medicine, (1996) 183/3 (1215-1228). ISSN: 0022-1007 CODEN: JEMEAV
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
C.B-17 scid/scid (severe combined immunodeficiency [SCID]) mice inoculated with peripheral blood lymphocytes from **Epstein-Barr** virus (***EBV***)-seropositive donors, or with **EBV**-transformed lymphoblastoid B cell lines (**EBV**-LCL), develop lethal human ***EBV*** + B cell lymphoproliferative disorders (**EBV**-LPD) with characteristics similar to those arising in immunodeficient patients. Using this model, we examined the capacity of human effector cells to control human ***EBV*** -LPD. SCID mice received rabbit anti-asialo GM1 antiserum to abrogate endogenous natural **killer-cell** function.
Preliminary experiments showed that adoptive transfer of peripheral blood mononuclear cells (PBMC), purified T cells, **interleukin** (**IL**) **2**-activated PBMC or anti-CD3-activated T cells derived from ***EBV*** -seropositive donors did not result in improved survival of treated mice (in vivo effector/target ratio 2:1 to 1:1). In contrast, **EBV**-specific cytotoxic T lymphocytes (CTL), derived from **EBV**-seropositive donors and expanded in vitro, exhibited strong **EBV**-specific and HLA-restricted activity both in vitro and in vivo. SCID mice inoculated intraperitoneally with autologous but not with HLA-mismatched ***EBV*** -LCL had significantly improved survival relative to untreated mice after inoculation of **EBV**-specific CTL either intraperitoneally ($P<0.001$) or intravenously ($P<0.001$) (in vivo effector/target ratio 1:1). SCID mice bearing large subcutaneous EEBV+ tumors and treated intravenously with 107 ***EBV*** -specific CTL achieved complete tumor regression. Both CTL- and CTL-plus-IL-2-treated mice survived significantly longer than untreated animals or animals treated with IL-2 alone ($P=0.004$ and $P<0.02$, respectively). SCID mice bearing two subcutaneous **EBV**+ tumors, one autologous and the other HLA mismatched to the **EBV**-specific CTL donor, had regression of only the autologous tumor after intravenous infusion of 107 **EBV**-specific CTL. Moreover, we could demonstrate preferential homing of PKH26-labeled **EBV**-specific CTL to autologous but not to HLA-mismatcheed **EBV**+ tumors as early as 24 h after intravenous adoptive transfer. Immunophenotypic analyses also demonstrated preferential infiltration of T cells into the autologous **EBV**+ tumor in SCID mice bearing both the autologous and either fully HLA-mismatched or genotypically related haplotype-sharing **EBV**+ tumors. The human T cells infiltrating ***EBV*** + tumors were CD3+ and, predominantly, CD8+CD4. Our results indicate that **EBV**- specific CTL preferentially localize to and infiltrate EEBV+ tumors bearing the appropriate HLA antigens and thereafter induce targeted regressions of disease.

CONTROLLED TERM: Medical Descriptors:
*cytotoxic t lymphocyte
*xenograft
*lymphoproliferative disease: TH, therapy

animal experiment
animal model
article
controlled study
effector cell
epstein barr virus
human
human cell
immune deficiency
immunophenotyping
immunotherapy
mouse
nonhuman
priority journal
scid mouse
survival
t lymphocyte activation
t lymphocyte subpopulation
tumor regression
Drug Descriptors:
*HLA antigen
*cd3 antigen
*cd4 antigen
*cd8 antigen

L10 ANSWER 136 OF 472 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:241363 BIOSIS
DOCUMENT NUMBER: PREV200200241363
TITLE: Infusion of autologous **Epstein-Barr** Virus (**EBV**)-specific cytotoxic T cells can treat chronic active **EBV** infection.
AUTHOR(S): Savoldo, Barbara (1); Huls, Helen M. (1); Liu, Zhengsheng (1); Volk, Hans D.; Reinke, Petra; Sabat, Robert; Babel, Nina; Jones, James F.; Gee, Adrian P. (1); Brenner, Malcolm K. (1); Heslop, Helen E. (1); Rooney, Cliona M. (1)
CORPORATE SOURCE: (1) Cell and Gene Therapy, Baylor College of Medicine, Houston, TX USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 502a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
ABSTRACT:
The term chronic active **Epstein-Barr** Virus infection (CAEBV) syndrome covers a heterogeneous spectrum of **EBV**-related disorders characterized by chronic fatigue, fever, lymphadenopathy and/or hepato-splenomegaly, associated with abnormal antibody titers to **EBV**. Compared to the severe and usually fatal forms seen in Japan, in the western hemisphere this syndrome is a severely debilitating but usually non-life threatening disorder. However, current therapies with anti-viral, anti-inflammatory and steroidal drugs are often limited by severe adverse effects. Since it has been demonstrated that adoptive transfer with **EBV**-specific cytotoxic T cells (CTL) can restore **EBV**-specific immunity in immunocompromised patients, we have applied this approach to the treatment of this persistent active **EBV** infection. Using multiple stimulations with autologous lymphoblastoid cell lines (LCL) in the presence of **IL-2**, we have regularly been able to generate anti-**EBV** effector cells ex-vivo from a total of eight affected patients. The CTL consisted mainly of CD3+CD8+ cells which kill autologous but not HLA-mismatched LCL or a lymphokine activated natural **killer cell** line (mean 62% vs 9% vs 24%, at 20:1 effector: target ratio, respectively; $p<0.001$). Moreover, the preincubation of autologous LCL with the anti-HLA class I monoclonal antibody reduced killing activity (mean inhibition 36%, $p<0.001$). ***EBV*** -specific CTL have been infused into four patients, with 4 to 12-year histories of disease not responding to anti-viral or anti-inflammatory therapy. In all four, one to three injections of 2X107/m2 of **EBV**-specific CTL resulted in normalization of the pattern of anti-**EBV** antibodies. Fatigue and malaise resolved and fever disappeared in all patients. Lymphadenopathy, present in two patients, completely regressed and the severe splenomegaly, present in one of them, was reduced from 1700 ml to 450 ml (calculated by ultrasound scan). This patient in particular was able to return to work after five years of absence, though his chronic renal failure induced by the steroid and non-steroid anti-inflammatory drugs used in the 5 years before the immunotherapy with CTL did not improve. No toxicity was observed and the clinical responses have persisted for >6 to >24 months after infusion. In addition, there was a trend for an increase in the **EBV**-CTL precursor frequency and expression of Th1-cytokines. Therefore, adoptive immunotherapy with autologous **EBV**-specific CTL may represent a safe and feasible alternative treatment for patients affected by CAEBV infection syndrome.
CONCEPT CODE: General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies *15002
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004

Virology - Animal Host Viruses *33506
Immunology and Immunochemistry - General; Methods *34502
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
Medical and Clinical Microbiology - Virology *36006

BIOSYSTEMATIC CODE: Herpesviridae 02612
Hominidae 86215

INDEX TERMS: Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Infection

INDEX TERMS: Parts, Structures, & Systems of Organisms
CD3 positive CD8 positive cell: blood and lymphatics, immune system; **Epstein-Barr** virus-specific cytotoxic T cell [**EBV**-specific cytotoxic T cell]: blood and lymphatics, immune system

INDEX TERMS: Diseases
chronic active **Epstein-Barr** virus infection [chronic active **EBV** infection]: symptom, therapy, viral disease

INDEX TERMS: Miscellaneous Descriptors
lymphoblastoid cell line; Meeting Abstract; Meeting Poster

ORGANISM: Super Taxa
Herpesviridae: Animal Viruses, Viruses, Microorganisms; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGANISM: Organism Name
Epstein-Barr virus [**EBV**] (Herpesviridae): pathogen; human (Hominidae): host, patient

ORGANISM: Organism Superterms
Animal Viruses; Animals; Chordates; Humans; Mammals; Microorganisms; Primates; Vertebrates; Viruses

L1 ANSWER 49 OF 50 COPYRIGHT 2003 Gale Group on STN

ACCESSION NUMBER: 96:275996 NLDB
TITLE: Immunotherapy (Antiviral) "Long-Term Repopulation with EBV-Responsive T Cells Following Adoptive Transfer of Gene-Modified Virus-Specific T Lymphocytes." C. Li, C.Y.K. Ng, C.A. Smith, S. Loftin, R.A. Krance, M.K. Brenner, C.M. **Rooney** and H.E. Heslop. St. Jude Children's Research Hospital, Memphis, Tennessee.
SOURCE: Gene Therapy Weekly, (17 Jun 1996) .
ISSN: 1078-2842.
PUBLISHER: Charles W Henderson
DOCUMENT TYPE: Newsletter
LANGUAGE: English
WORD COUNT: 284
TEXT:
According to an abstract submitted by the authors to the 87th Annual Meeting of the American Association for Cancer Research, held April 20-24, 1996, in Washington, D.C., "Adoptive transfer of antigen specific cytotoxic T cells (CTL) is a safe and effective therapy for certain viral infections (e.g. ***Lancet*** 1995, 345:9-13) and may prove useful in eradication of tumor cells. Whether or not the infused T cells persist for extended periods, and retain their ability to expand in response to antigenic stimulation is not known. We have addressed this question by giving donor derived EBV-specific cytotoxic T cell lines (10(7)/m(2)x4) to 19 patients following T cell depleted BMT from a matched unrelated donor or mismatched family member. Up to 5% of the cells were genetically marked with the neoR gene. In all patients, administration is associated with the appearance of marker positive T cells in the peripheral blood, and with the development of an MHC restricted anti-viral response. The cytotoxic T lymphocyte precursor frequency rises 5 to 100 fold, to enter the high normal range. If peripheral blood lymphocytes are cultured with donor EBV(+) lymphoblasts, the marker gene once again becomes detectable in both the CD4(+) and CD8(+) population. The restimulated cells retain a high level of MHC restricted cytotoxicity against EBV(+) target cells. Evidence for in vivo function was obtained from a patient in whom a 1000-fold rise in EBV DNA levels in peripheral blood 18 months after CTL infusion was rapidly followed by the reappearance of neoR positive EBV-specific T cells in the circulation. Hence adoptive transfer of CTL leads to long-term repopulation with cells that retain antigen specificity and expand upon challenge with the pathogen."

Subscription: $1,195.00 per year as of 8/96. Published 52 times per year. Contact CW Henderson, PO Box 830409, Birmingham, AL 35283-0409. Phone (800) 633-4931.

CONTROLLED TERM: MH Medical and Health